Safety and efficacy of renal denervation utilizing standard bidirectional EP catheter: preliminary Vietnamese findings

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ABSTRACT

Renal denervation (RDN) is a safe and effective treatment for hypertensive patients. However, data on its use with standard electrophysiology catheters, particularly from low- and middle-income countries, are limited. This study aimed to evaluate the acute safety and short-term efficacy of RDN in hypertensive patients using standard EP catheters from Vietnam. A prospective study was conducted from May 2023 to May 2024 at the Viet Nam National Heart Institute, Vietnam. A total of 22 patients (mean age 52.87±19.86 years, 12 male) with resistant hypertension underwent RDN by utilizing a standard bidirectional steerable radiofrequency (RF) ablation catheter with a 7 Fr diameter (Abbott, Chicago, IL, USA). Low-power RF applications have been applied along the length of both renal arteries. Renal ultrasound, blood tests, and 24-hour ambulatory blood pressure (BP) were checked at baseline, at 1 month, and at 3 months following RF ablation. The success rate of the renal artery approach with a standard bidirectional EP catheter was 100% (22/22 patients). The mean reduction of 24-hour ambulatory BP, and ambulatory daytime BP were respectively -8.72/-6.04 mmHg and -8.00/-6.09 mmHg at 1 month and -15.59/-9.22 mmHg and -15.27/-10.18 mmHg at 3 months ($p<0.05$ for systolic and diastolic BP) with unchanged medication. No severe complications were reported during the procedure and follow-up. Our initial results indicate the safety and efficacy of RDN as shown by a significant reduction of mean 24-hour ambulatory BP in comparison to baseline during short-term follow-up.

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Introduction

It is believed that between 13% and 30% of people receiving medication treatment for hypertension also have resistant hypertension. Given that the risk of cardiovascular death doubles with every 20/10 mmHg increase in blood pressure (BP), this scenario constitutes a serious worldwide health concern. Although recent research has looked at device-based or procedural therapy, there are not many options for treatment for these patients. Renal sympathetic denervation (RSDN) is a catheter-based, percutaneous technique to disrupt the renal afferent and efferent nerves. There is evidence to suggest that prolonged activation of the sympathetic nervous system may be a contributing factor in resistant hypertension.[1] The first "proof-of-principle" clinical trial of transcatheter renal denervation (RDN) showed that treatment was associated with a marked reduction in BP in patients with resistant hypertension. While the results of the first pivotal trial of the first generation of radiofrequency-based RDN (SYMPLICITY HTN-2) were positive, this was an open-label trial with no sham control group. Subsequently, the first sham-controlled trial of radiofrequency RDN, SYMPLICITY HTN-3, failed to document a significant difference in systolic BP (SBP) reduction between RDN and sham groups at 6 months after the procedure in patients with resistant hypertension.

Since then, there have been many other sham-controlled trials of both the second generation of radiofrequency- and ultrasound-based RDN in a variety of hypertensive patient populations. Many of these have reported positive findings, with significantly greater reductions in BP in the RDN *versus* the control group.[2,3]

Based on the available data from the above trials, the US Food and Drug Administration approved both the SYMPLICITY SPYRAL radiofrequency RDN system and the PARADISE ultrasound RDN system for the adjunctive treatment of hypertension in patients with hypertension for whom lifestyle modifications and antihypertensive drug therapy do not adequately control BP. The 2023 European Society of Hypertension guidelines make a class II recommendation for the use of RDN in patients with uncontrolled hypertension, and consensus statements about RDN have been published by several societies and working groups.[4]

Since these particular RDN catheters are hard to obtain in low- and middle-income countries, we utilized a standard bidirectional ablation catheter for RSDN with BP reductions observed in several studies.[5,6] Our study was conducted to assess the safety and efficacy of utilizing a standard bidirectional steerable radiofrequency (RF) ablation catheter (Abbott, Chicago, IL, USA) to treat resistant hypertension in a low-middle-income country.

Materials and Methods

Ethical considerations

The study was conducted following the Declaration of Helsinki, and it was approved by the Institutional Review Board of Hanoi Medical University under decision No. 796/GCN-HĐĐĐNCYSH-ĐHYHN dated March 22nd, 2023. Written informed consent was obtained from the patients before participating in the study. The investigators were responsible for protecting the privacy and confidentiality of patients as per Vietnam's regulations and Good Clinical Practice.

Patients

We included 22 patients with drug-resistant hypertension. Resistant or uncontrolled hypertension is defined as follows: office BP (≥140/90 mmHg) and/or out-of-office BP (24 h ambulatory BP≥130/80 mmHg, daytime ambulatory BP≥135/85 mmHg, nighttime ambulatory BP≥120/70 mmHg, morning/evening home BP≥135/85 mmHg, or nighttime home BP≥120/70 mmHg) despite adequate lifestyle modification and treatment with maximum tolerated dosages of three or more antihypertensive agents from different classes, including a diuretic (except where there is a contraindication for use of diuretics). Patients with vascular malformations that would prevent catheter insertion were excluded. Patients with renovascular abnormalities (including severe renal artery stenosis, previous renal angioplasty, or dual renal arteries) or in the condition of acute infection, coagulopathy, severe systemic disease, intracardiac thrombosis or known secondary causes of hypertension were excluded from intervention.[2,3]

Study procedure

Prior to the ablation procedure, patients underwent baseline evaluations that included physical examination, review of medications, basic blood chemistries (including serum creatinine and proteinuria), and 24-hour ambulatory BP. All patients were observed for at least 3 months on appropriate antihypertensives to ensure compliance with the medication regime. Renal ultrasounds were done by specialists to look for renal artery diameter, length, and stenosis.

The procedure was performed under local anesthesia and conscious sedation. We performed bilateral common femoral artery punctures. Renal artery stenosis was excluded by renal angiogram *via* left femoral access (Judkins Right catheter; Boston, MA, USA). After a second puncture of the right femoral artery, a standard bidirectional steerable RF ablation catheter with a 7 Fr diameter (Abbott, Chicago, IL, USA) was introduced into the renal artery. Using this bilateral approach, we were able to inject diluted contrast dye into the renal artery during ablation. RF ablation was performed in both renal arteries consecutively. We applied low-power RF applications along the length of both renal arteries consecutively (separated both longitudinally and rotationally to achieve a circumferential lesion). Ablated points were implemented via the main trunks and post-first bifurcation of renal branches. Impedance and temperature were continuously monitored during RF ablation. Intravenous heparin modified by weights (100 units/kg). Subsequently, all patients received aspirin 100 mg per day for 3 months. Follow-up assessments at 1 and 3 months consisted of office BP measurement, 24-hour ambulatory BP, physical examination, blood chemistries (including serum creatinine and proteinuria), and adverse events.

Safety endpoints included the absence of any device-related major complication, defined as any periprocedural major vascular complication including renal artery perforation or dissection, any significant embolic event resulting in target organ damage, major bleeding as defined by the Bleeding Academic Research Consortium classification, end-stage renal disease, stroke, acute myocardial infarction, and any cause of death within 1 month of the procedure. Any other complication related to the procedure was classified as minor.

The efficacy endpoint was determined by the interindividual change in ambulatory blood pressure monitoring (ABPM) from baseline to three months after the procedure.

According to the literature, patients were defined as responders if a reduction of 5 mmHg in daytime SBP was a clinically meaningful reduction at their last available follow-up visit.

Statistical analysis

Continuous variables are expressed as mean ± standard deviation. Categorical data are summarized as frequencies and percentages. Differences in BP between baseline and follow-up were analyzed using the paired Student's *t*-test for continuous variables. A $p<0.05$ was considered statistically significant. The statistical analyses were computed with SPSS© (SPSS Inc., Chicago, IL, USA) statistical software.

Results

From May 2023 through May 2024, 22 patients with drug-resistant hypertension underwent RDN (mean age 52.09±13.08 years, 12 male). Some of the patients had severe comorbidity (13 patients with diabetes mellitus, 5 patients with coronary artery disease, and 5 patients with chronic renal

insufficiency defined as serum creatinine levels >130 µmol/l). Baseline parameters of patients are shown in Table 1. Ablation points were performed within each renal artery with a maximum duration of up to 1 min for each point and power ranges of 8-12 watts.

Energy delivery was titrated to a maximum of 8-12 watts. Electrode temperature (mean 47±6°C) and impedance (mean 225±24 ohms) were monitored continuously during each energy application. Total ablation points were 35.48±5.87 (average ablation points of right renal artery and left renal artery were consecutively 18.14±3.12 and 17.24±3.04). The mean procedure time was 75.48±5.88 min. The amount of contrast ranges 150.3±30.4 mL. Intravenous narcotic and sedative drugs (fentanyl titrated up to 0.15 mg and midazolam 4 mg) were administered for the diffuse visceral abdominal pain occurring during RF ablation. The pain was limited to the duration and power of RF energy delivery. After the procedure, a final renal angiogram was performed to check whether ffocal renal artery dissection or rupture immediately after RF energy delivery exit or not (Figure 1).

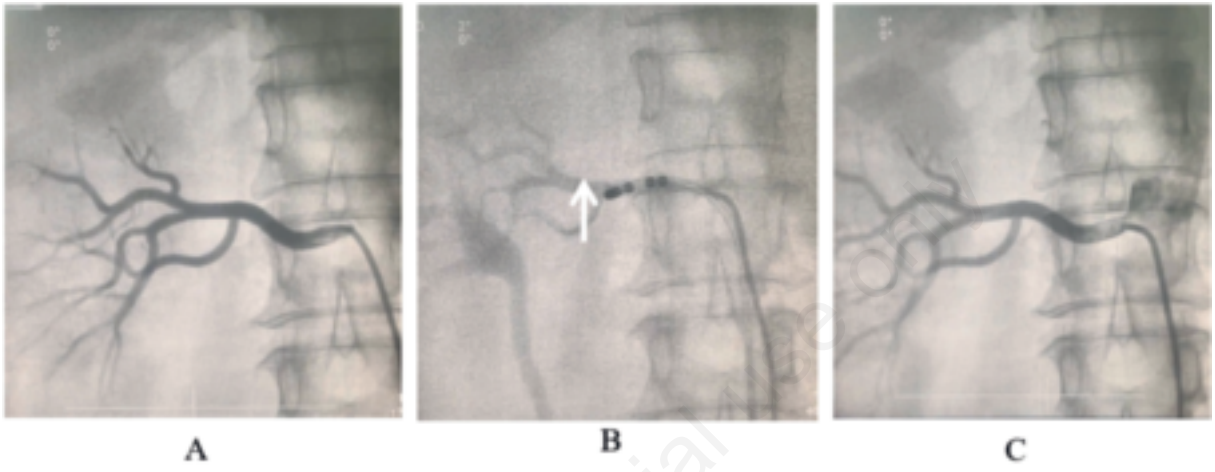

Figure 1. Angiography of the right renal artery at baseline (A), RF ablation point (white arrow) (B), and immediately following the procedure (C). No significant stenosis of the renal artery was observed.

Table 1. Baseline patient demographics.

Variable	Mean ± SD or n (%)
Male (sex)	12 (54.54)
Mean age (years)	52.09±13.08
Body mass index	26.33±0.58
Creatinin (µmol/L)	104.77±55.33
Left ventricle ejection fraction (%)	62.64±7.03
Comorbidities	
Diabetes mellitus	13 (31.25)
CAD	5 (16.6)
Prior stroke	4 (12.5)
Chronic renal insufficiency (Creatinine>130 µmol/L)	5 (33.3)
Number of antihypertensive medication	4.3±0.7
ACE-I	3 (37.5)
ARB	17 (43.75)
Beta-blockers	18 (81.25)
Diuretics	22 (100)
Calcium-channel blockers	22 (81.25)
Centrally acting sympatholytic	10 (75)
24 h ambulatory systolic BP (mmHg)	142.05±13.52
24 h ambulatory diastolic BP (mmHg)	90.95±11.38
Ambulatory daytime systolic BP (mmHg)	138.95±12.98
Ambulatory daytime diastolic BP (mmHg)	91.22±11.64
Ambulatory nighttime systolic BP (mmHg)	143.32±17.51
Ambulatory nighttime diastolic BP (mmHg)	89.64±13.52

CAD, coronary artery disease; ACE-I, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; BP, blood pressure.

We did not observe vascular complications during follow-up. No patient was lost to follow-up.

The parameters of ambulatory BP at baseline and during follow-up are listed in Table 2. Patients were taking a mean number of 4.27±0.7 antihypertensive medications at baseline, 4.27±0.7 at 1 month, 4.14±0.69 at 3 months (Table 2).

The mean reduction of 24-hour ambulatory BP, and ambulatory daytime BP were -8.72/-6.04 mmHg, -8.00/-6.09 mmHg at 1 month, and -15.59/-9.22. mmHg, -15.27/-10.18 mmHg at 3 months ($p<0.03$ for systolic and diastolic BP), respectively with no medication escalation (Table 3).

The renal function assessed by serum creatinine and proteinuria remained unchanged from baseline. Renal duplex sonography during follow-up found no evidence of renal artery stenosis or other abnormalities in all patients.

According to the definition of response by a mean reduction in ambulatory daytime SBP of >5 mmHg in ABPM, we found that the proportions of patients who were responders were 12/22 (54.55%) at 1 month and 18/22 (81.82%) at 3 months. In the case of a mean reduction in 24 h ambulatory SBP of >5 mm Hg in ABPM, the responder rates were 13/22 (59.01%) at 1 month and 19/22 (86.36%) at 3 months.

Discussion

In our study, we found that low-dose RF energy ablation of the renal artery in order to perform sympathetic RDN by using a standard bidirectional steerable RF ablation catheter (Abbott, Chicago, IL, USA) is feasible and safe during short-term follow-up in a real-life, unselected population of patients with resistant hypertension.[7]

Despite the relatively small number of patients (n=22), this is the largest series of RDN cases performed in Vietnam to date.

The mean reduction of 24 h ambulatory BP and ambulatory daytime BP was respectively -15.59/-9.22 mmHg, -15.27/-10.18 mmHg at 3 months ($p<0.05$ for systolic and diastolic BP) with unchanged medication, which is compatible with the results of the trial DENERVHTA 2016, RADIOSOUND HTN 2019 (mean reduction of ambulatory SBP -15.8 mmHg, -13.2 respectively during 3-month follow up).[2,3]

In our study, 18 of 22 treated patients (81.82%) could be classified as responders to RSDN defined by a reduction in ambulatory daytime SBP of 5 mmHg or more at three months after RF ablation.[5,8] In several pivotal studies,[9,10] the magnitude of response was unpredictable, with some patients over-responding and only about 70-80% presenting with any BP reduction after RDN. The time points of data assessment (3 *versus* 2 months in RADIANCE Trials or 6 months in SYMPLICITY SPYRAL Trials), nature of energy (ultrasound, radiofrequency) as well as the ablation points, distal ablation might be the reasons for the different responder rates in the studies.[11-13]

In fact, during the follow-up period of the RADIANCE trials, the BP reduction improved 2 months following RDN

Table 2. Post renal denervation ambulatory blood presure during follow-up.

Variable	Mean ± SD/n				
	Baseline (mmHg)	1 month (mmHg)	p	3 month (mmHg)	p
24 h ambulatory systolic BP (mmHg)	142.05±13.52	133.68±14.18	0.0013	126.57±13.59	<0.001
24 h ambulatory diastolic BP (mmHg)	90.95±11.38	85±11.21	0.002	82.09±11.14	<0.001
Ambulatory daytime systolic BP (mmHg)	138.95±12.98	133.33±13.38	0.002	126.48±13.83	<0.001
Ambulatory daytime diastolic BP (mmHg)	91.22±11.64	85.76±10.87	0.005	81.38±10.92	<0.001
Ambulatory nighttime systolic BP (mmHg)	143.32±17.51	132.57±16.4	0.026	124.57±14.65	<0.001
Ambulatory nighttime diastolic BP (mmHg)	89.64±13.52	84.05±13.05	0.04	80.52±11.47	<0.001
Number of antihypertensive medications	4.27±0.7	4.27±0.7	>0.05	4.14±0.06	0.082

BP, blood pressure.

Table 3. Mean reduction of blood pressure at 1-month follow-up, 3-month follow-up.

Variables	Mean reduction of blood pressure with time	
	1 month (mmHg)	3 month (mmHg)
24 h ambulatory systolic BP (mmHg)	8.72±10.26	15.59±11.09
24 h ambulatory diastolic BP (mmHg)	6.04±7.09	9.22±6.35
Ambulatory daytime systolic BP (mmHg)	8.00±9.36	15.27±10.58
Ambulatory daytime diastolic BP (mmHg)	6.09±6.97	10.18±7.67
Ambulatory nighttime systolic BP (mmHg)	12.32±15.12	19.5±17.08
Ambulatory nighttime diastolic BP (mmHg)	6.36±9.81	9.9±9.16

BP, blood pressure.

in comparison to the 3-month follow-up visit. In contrast, the improvement of blood reduction in SYMPLICITY SPYRAL trials was observed 6 months following RDN.[8,9] The differences in the results of the studies might be due to technical aspects and the use of the energy.

Contrary to the currently published trials, we describe for the first time the use of a standard bidirectional steerable RF ablation catheter for RSDN.[5,7,14] The outstanding advantages of catheters are the cost and the familiar performance of the catheters used in the studies (*e.g.*, shaft torsion and stiffness characteristics as well as tip buckling and bond strengths), accompanied by the broad availability of the standard bidirectional steerable RF ablation catheter.[1,6] With our technique, it is possible to use the standard equipment of the electrophysiology laboratory (*e.g.*, standard RF generator) to facilitate the renal artery approach. The handling of the EP catheter is easy if the examiner is familiar with this technique and the performance of the catheter is non-traumatic, as shown during RF ablation of the coronary venous system and the aortic sinus for ablation of ventricular arrhythmias. During manipulation, we could ensure circumferential ablation by up-and-down tip contact movement and then rotation (180°).

The parameters during ablation are similar to those of Dirk Prochanau *et al*. which was conducted with a shorter RF application time (1 min each of 8-12 watts).[7,15,16]

No serious complications related to the device or procedure have been observed. Serum creatinine and proteinuria as markers of renal function remained unchanged from baseline. Renal duplex sonography during follow-up found no evidence of renal artery stenosis or other abnormalities in all patients. These findings are also in agreement with recent published trials.[17,18]

Limitations

We acknowledge several limitations of our analysis. Firstly, this is a single-center study design. Secondly, the number of patients is quite small, and no control group in the study. Furthermore, the follow-up time is short.

However, more research in a larger population is necessary to determine whether using a standard EP catheter for RSDN actually improves the long-term outcome in resistant hypertension.

Conclusions

As shown during short-term follow-up, our preliminary results indicate that RDN with a standard RF ablation catheter can be utilized safely to significantly reduce mean 24 h ambulatory BP in resistant hypertension.

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